REMARKS

Applicants have amended the specification and claims to more particularly define the invention taking into consideration the outstanding Official Action. The specification has been amended on pages 45 and 47 of the Bibliography to correct the page numbers of the references. In addition, applicants have added a proper Sequence Listing (paper copy and computer readable form thereof) which is found at the end of this Amendment as required in the Official Action. The below signed attorney hereby states that the submission submitted herewith in accordance with 37 CFR § 1.821(g) does not include any new matter. The below signed attorney also hereby states that the content of the attached paper copy of the sequence listing and the attached computer readable form thereof submitted in accordance with 37 CFR § § 1.821(c) and (e), are the same.

Applicants have amended claims 13, 22 and 23. The claims now remaining in the application are claims 13-35 and 40. Applicant most respectfully submit that all the claims now present in the application are in full compliance with 35 U.S.C. §112 and are clearly patentable over the references of record.

Applicants have amended claim 13 to further clarify that the claimed method of treatment is limited to not simply all of the compounds depicted by formulae (I) and (II), but compounds selected from this group and which fulfill the further requirement of facilitating the disruption of a chelated metal cation domain of a protein encoded for/by an MPV gene. Thus, only compounds of formula (I) and (II) which facilitate the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene are contemplated by claim 13. In addition, it should be noted that claim 13 also contemplates pharmaceutically acceptable derivatives of suitable compounds of formulae (I) and (II) as indicated in the specification at page 10, line 27 and page 21, lines 1-11.

The Examiner objects to claim 22 under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants have amended claim 22 to be dependent upon claim 20 and not on claim 21.

Accordingly, it is most respectfully requested that this objection be withdrawn in view of the amendment to the claim.

Claim 23 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. After careful consideration of this rejection, claim 23 has been amended to replace the phrase "at least one of R^1-R^4 is as depicted in any compound in Groups 1 to 6 as defined herein" with "at least one of R^1-R^4 as selected from the group consisting of:" thereby obviating the rejection that claim 23 lacks antecedent basis. Therefore, it is most respectfully requested that this rejection be withdrawn.

The rejection of claim 40 under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the specific compounds represented by formula (I) having at least 30% zinc release in a TSQ assay and the activity of inhibiting or reducing the binding of an E6 protein to E6AP or E6BP and cytotoxic effects on HPV containing cell lines, does not reasonably provide enablement for the term "a compound capable of facilitating the disruption of a chelated metal cation domain of protein encoded for by an MPV gene to a mammal in need thereof" is most respectfully traversed.

The Examiner has rejected claim 40 on the basis that the skilled person would not be able to determine what is a "compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene" without undue experimentation. In this regard, Applicants would like to draw the Examiner's attention to the disclosure at pages 21-23 of the specification. As pointed out in lines 24-29 of page 21, through to lies 1-6 of page 22, the potential suitability of a compound can be determined by directly or indirectly measuring the amount of a metal cation released when the compound is contacted with a protein molecule containing a chelated metal cation domain. A number of possible methods of measuring the released metal cation are described: namely TSQ assay, determining the absence or otherwise of binding of the E6 protein to E6AP or E6VP (BIACORE assay) and incubation of the MPV-infected cells with WSTI. Means of performing each of the TSQ, BIOCORE and WSTI assays are

described in the Examples 2, 3 and 5. Furthermore, the specification oat pages 23-24 indicates that particularly preferred compounds fulfill the requirements of 2 or more of the described tests. Thus, it is submitted that whilst the person of ordinary skill might have to perform some experimentation, i.e. testing a compound according to one or ore of the described assays, such experimentation would not be considered to be undue since suitable guidance and instruction as to how to perform these assays is provided in the specification. By subjecting any compound to the described tests, one of ordinary skill in the art would easily and readily be able to determine whether a compound falls within the scope of claim 40 or not.

Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ 2d at 1404 (Fed. Cir. 1988). See also United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 13, 14, 17-20, 23-35 and 40 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been carefully considered but is most respectfully traversed.

The Examiner has rejected claims 13, 14, 17-20, 23-35 and 40 as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. In particular, the Examiner alleges that: (I) it is not clear whether all the compounds of formulae (I) and (II) identified by the assays described would have the desired cytotoxic effects on HPV-16+ and HPV18+ cell lines; (ii) whether the claimed compounds capable of facilitating disruption of the HPV E6 and E7 zinc fingers are going to be effective in inhibiting growth of HPV containing cell lines other than the exemplified HPV 16+ and HPV 18+ lines; and (iii) whether the study of using C16 to inhibit growth of HPV 16+ and HPV 18+ cell lines can be extrapolated to the defined method of treating all diseases caused or exacerbated by an MPV.

First, while the Examiner has noted that a few compounds are active in the TSQ and BIACORE assays but have not been identified as being active in the WST assay, one cannot necessarily conclude that such compounds will not have the desired therapeutic effect. Possible causes of observed non-activity (or non-specific activity) in the WST assay may include inefficient penetration of the compounds into the cells or intracellular stability of the compounds being affected by intracellular factor, but this does not automatically mean that they would not be useful in therapy. One of ordinary skill in the art would recognize that such factors might be overcome by administering the compound as an appropriate pharmaceutically acceptable derivative (see page 21 of the specification). Thus, one of ordinary skill in the art would recognize that although compounds which exhibit activity in all 3 of the described assays might be preferred (see page 23, lines 21-26) other compounds of formulae (I) and (II) administered as a

pharmaceutically acceptable derivative may be effective in inhibiting the growth of MPV cell lines. This could be determined by routine experimentation.

In addition, the Examiner questions whether the ability to disrupt zinc fingers in HPV 16 and 18 positive cell lines could be extrapolated to other HPV positive cell lines and whether this can reasonably lead to the conclusion of the claimed method of treatment. HPV genomes contain eight genes, among them the oncogenes E6 and E7 which encode the E6 and E7 oncoproteins respectively. The oncoproteins E6 and E7 of different HPB types are homologous and have similar functions. It is well established in the scientific literature that HPV E6 and/or E7 proteins are essential for the formation and persistence of HPV-associated lesions and that the zinc fingers of HPV E6 and/or E7 are required for their cellular function. In this regard, see the publications 1-20 listed in the attached Appendix (Publications 1, 3, 4, 6-11 and 13 were submitted and cited in the previously submitted Supplemental Information Disclosure Statement dated July 23, 2001 and the remaining publications numbers 2, 5, 12 and 14-20 are submitted herewith and are listed on the accompanying form 1449). These are not cited as references but in support of the level of one of ordinary skill in the art. No fee is therefore required.

Thus, having the knowledge that the E6 and/or E7 zinc fingers are essential for cellular function, one of ordinary skill in the art would recognize that a compound which disrupts the E6 and/or E7 zinc fingers would reasonably be expected to treat a disease or condition caused by an HPV. Therefore, although only certain compounds have been shown to inhibit the growth of HPV16-positive and HPV18-positive cell lines, it is a reasonable expectation that a compound which is shown to disrupt the E6/7 zinc fingers will affect the growth and viability of other mammalian papilloma viruses and thus be useful in the claimed therapeutic treatment. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claim 40 under 35 U.S.C. 102(b) as being anticipated by Tran et al. has been carefully considered but is most respectfully traversed.

The Official Action alleges this document teaches the use of antisense ODN as a compound inherently capable of facilitating the disruption of a chelated metal cation

domain. However, the antisense concept involves the use of short complementary oligonucleotides to interfere with the function of mRNAs. Hybridization of the antisense ODN with the target RNA by complementary base pairing provides high specificity and binding affinity resulting in the "inhibition of expression of the proteins products" (see enclosed references cited below) and not "disruption of a chelated metal cation domain of a protein encoded for by the MPV gene", as would be appreciated by one of ordinary skill in the art to which the invention pertains. In this regard the examiner's attention is directed to the following three publications (copies enclosed herewith).

1. Stein, CA, and Cheng, YC. Antisense oligonucleotides as therapeutic agents – Is the bullet really magical? Science, 261:1004-1012, 1993.
2. Crooke, ST. Therapeutic applications of oligonucleotides. Biotechnology, 10:882-886, 1992.
3. Neckers, L, Whitesell, L, Rosolen, A, and Geselowitz, DA. Antisense inhibition of oncogene expression. Crit. Rev. Oncog., 3:175-231, 1992.

It is therefore submitted that Tran et al. do not describe the use of a compound which facilitates the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene and therefore, does not anticipate claim 40. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 13-15, 20, 31, 32, 33 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Rotstein et al. has been carefully considered but is most respectfully traversed.

The Examiner has rejected claims 13-15, 20, 31, 32, 33 and 40 on the basis that Rotstein et al. teach te use of disulfiram for treating or preventing cancer by treating papillomas, which are a population of putative precancerous lesions. The Examiner notes that although Rotstein et al. are silent as to the feature of disrupting the chelated metal cation domain, this is an inherent feature of the disclosure.

In Rotstein et al., GSH and disulfiram were shown to inhibit tumor progression by acting as antioxidants. This mechanism of actions is different from those of the compounds described in the subject application, which act to displace a chelated metal

cation from a protein encoded for by an MPV gene, in particular, to displace Zn from E6 and/or E7 proteins. For example, hydrogen peroxide, which is a very strong oxidant, is used as a positive control in the present studies (see page 22, lines 12-14) in displacing Zn from E6 or E7 protein, presumably by oxidizing the Cys in E6 or E7 which needs to be in the reduced form in order to bind Zn. In the case of Rotstein and Slaga's model, hydrogen peroxide acts in the opposite sense, i.e. to enhance the progression of papillomas to carcinomas. Therefore, from this example, it is very clear that the mechanisms of action for the present model and that described by Rotstein et al. are very different and that the disulfiram, as described is not acting to facilitate the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene. It is therefore submitted that Rotstein et al. do not anticipate the present claims. It is therefore most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the specification and claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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APPENDIX

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APPENDIX

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